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OVERCOMING THE LIMITS: INVESTIGATING THE FRONTIERS OF EPILEPSY RESEARCH

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ABSTRACT

Even after receiving corrective brain surgery for epilepsy, a sizable portion of individuals still experiences seizures. We are still unsure of the cause of this resistance to therapy. Therefore, we must thoroughly investigate epileptogenesis to develop a treatment for the difficult-to-treat form of epilepsy. Most research on drug-resistant epilepsy (DRE) to date has focused on reducing the levels of antiepileptic medications near their targets and disrupting the abnormal activity of receptors involved in synaptic transmission. This theory posits that local neurons utilize complex oscillatory circuits to attract distant neurons, which subsequently draw in even more distant neurons, resulting in hypersynchronous neuronal activity. Patients who experience ischemic and hemorrhagic strokes affecting the thalamus, basal ganglia, and/or their connections have been observed to exhibit involuntary movements, occurring in 1–4% of cases after a stroke. While dystonia is more common in children, hemichorea and hemiballismus are the most frequent movement disorders in adults following a stroke. Other movement problems observed after a stroke include vascular parkinsonism, myoclonus, asterixis, tremor, and stereotypies. Although a larger percentage of patients report that their symptoms have resolved, early detection and management are crucial due to the disabilities that result from these conditions, which include social, financial, and occupational burdens, as well as the need for effective treatment.

KEYWORDS: EEG, Cardiac Investigation, Population, Mortality, Levetiracetam.

INTRODUCTION

Epilepsy, a disorder with neurobiological, cognitive, psychological, and social repercussions, is characterized by the brain's persistent tendency to produce seizures. It affects more than 50 million people worldwide, and its origins remain largely unknown, leaving patients and doctors uncertain about the disease's genesis and the most effective treatment options. Numerous studies have focused on behavioral adjustment issues in epilepsy, particularly regarding depression, anxiety, quality of life (QOL), and stigma. Recent research indicates that patients with epilepsy experience depression at a moderate to high rate, ranging from 19% to 60%. Furthermore, the prevalence of mood disorders in epilepsy is reported to be higher than in other conditions, such as diabetes and asthma. Got it! Here's the corrected paragraph. For individuals with refractory epilepsy, vagus nerve stimulation (VNS) is a relatively new treatment option. The afferents of the vagus nerve first arrive at the nucleus tractus solitarii, which has several connections to numerous other parts of the brain, indicating a complex pattern of activity. Functional magnetic resonance imaging is used to study the localized changes in the EEG, brain perfusion, and activation patterns.

LAW OF EPILEPSY IN INDIA

The Hindu Marriage Act of 1955 and the Special Marriage Act of 1954 were modified by the Indian government in 1976. According to the 1976 Marriage Laws Amendment Act, a person who suffers from frequent episodes of epilepsy or insanity is not allowed to marry, and their marriage will be voidable, leading to divorce. Of the 70 million people with epilepsy (PWE) in the world, about 12 million are thought to live in India.

MORTALITY RATE OF EPILEPSY

In a recent five-year follow-up among the general population in Kolkata, an annual mortality rate of 7.6 per 100,000 and an age-standardized mortality rate (ASMR) of 2.58 for epilepsy were reported.

PATIENT POPULATION

The study included 18 JME patients, 13 of whom were female and 5 of whom were male. The age range was 10 to 46 years, with a mean age of 20.4 ± 9.4 years. The average age at which epilepsy first appeared was 13 years; all patients showed myoclonic and TCS symptoms. Both types of seizures always occurred within the first hour after waking up. The

patients' neurological tests were normal, and their EEG recordings showed the typical paroxysmal generalized activity with PSWC. In the UM group, the annual seizure frequency (TCS) was 1.2, while in the M group, it was 1.3. One week before the EEG registration, no patient had TCS. Only three individuals had been diagnosed with JME before being admitted to the trial. As a result, nearly all patients were not receiving any other AED treatment or a specialized AED for JME.

EPILEPSY SURGERY

Although the exact number of patients for whom surgery may be successful is unknown, it is thought to be just over 2% of the entire cohort. Surgery may be considered in up to 3,500 incident cases and 15,000 prevalent cases, with an incidence of 0.5% and a prevalence of 750,000 in the USA. For more than 20 years, the annual number of epilepsy surgeries has remained constant at about 1,500 cases. Long-term cost-effectiveness, prolonged remission, and the possibility of 86% of children and nearly half of adults discontinuing AEDs are all benefits of the treatment.

RESULTS

CLINICAL MATERIAL

The number of patients treated with experimental medications (only 418 patients received ZNS treatment, compared to nearly 900 patients receiving PGB) and placebos (ranging from 273 to 424 instudies including ZNS or LTG, respectively) varied somewhat (refer to Table 1).

Table 3 Characteristics of studies included in the analysis

Study	No. of pts drug/ placebo and model	No. of concomitant drugs	Daily dose (no. of pts treated per dose)[a]/no. of administrations	Speed of titration	Duration of double-blind phase (weeks)	Lower frequency limit of inclusion of CNS AEs
GBP						
US Gabapentin[22]	208/98, parallel	≤2	600 (53)—1200 (101)—1800(54) mg/t.i.d.	2 or 3 days	12	≥10%
Anhut et al.[23]	163/109, parallel	≤2	900(111)—1200(52) mg/t.i.d.	2 days	12	>5%
Yamauchi et al.[13]	127/82, parallel	≤2	1200(86)—1800(41) mg/t.i.d.	2 or 3 days	12	>3%
Chadwick et al.[24]	71/58, parallel	≤2	1200 mg/t.i.d.	2 weeks	14	≥3%
Sivenius et al.[21]	25/18, parallel	≤2	900(16)—1200(9) mg/t.i.d.	2 days	12	≥10%
Total GBP	594/365					
LEV						
Betts et al.[34,a]	80/39, parallel	≤3	2000(42)—4000(38) mg/b.i.d.	No tit	24	≥10%
Cereghino et al.[36]	199/95, parallel	≤2	1000(98)—3000(101) mg/b.i.d.	4 weeks	14	≥10%
Shorvon et al.[37]	212/112, parallel	≤2	1000(106)—2000(106) mg/b.i.d.	2 weeks	12	≥5%
Ben-Menachem and Falter[35]	181/105, parallel	1	3000 mg/b.i.d.	4 weeks	18	≥5%
Tsai et al.[14]	47/47, parallel	≤3	2000 mg/b.i.d.	2 weeks	14	≥5%
Total LEV	719/398					
LTG						
Sander et al.[27]	21, crossover	≤3	100 or 200 mg/b.i.d.	2 weeks	12 (each treatment)	All AE
Schapel et al.[29]	41, crossover	≤2	150 or 300 mg/b.i.d	1 week	12 (each treatment)	All AE
Loiseau et al.[26]	25, crossover	≤2	150 or 300 mg/b.i.d	1 week	8 (each treatment)	All AE
Boas et al.[32]	56, crossover	≤3	75—400 mg/b.i.d	1 week	12 (each treatment)	≥10%
Smith et al.[30]	81, crossover	≤2	200—400 mg/b.i.d	2 weeks	16 (each treatment)	≥3%
Jawad et al.[25]	24, crossover	≤2	75—400 mg/b.i.d	4 weeks	12 (each treatment)	≥5%
Matsuo et al.[28]	143/73, parallel	≤3	300(71)—500(72) mg/b.i.d	4 weeks	24	≥10%
Messenheimer et al.[31]	98, crossover	≤2	400 mg/b.i.d	3 weeks	14 (each treatment)	≥10%
Beran et al.[33]	26, crossover	≤4	75 or 150 mg/b.i.d	3 weeks	8 (each treatment)	≥8%
Total LTG	494/424					
OXC						
Barcs et al.[38]	519/173, parallel	≤3	600(168)—1200(177)—2400(174) mg/b.i.d.	2 weeks	26	≥10%
Total OXC	519/173					

LEVETIRACETAM

Five double-blind studies using this medication in adult patients were found (see Table 3). In

every instance, the design of these studies was parallel. Titration was typically carried out over two to four weeks, although in one trial, it wasn't done at all. The double-blind phase lasted anywhere from 12 to 24 weeks. Patients receiving treatment at a dosage of 4,000 mg per day were not included in the RD calculation because this is not a recommended dosage (see above). Patients taking this medication experienced six of the previously listed CNS adverse events: depression, diplopia, dizziness, fatigue, headache, and somnolence. According to the trend test conducted on doses ranging from 1,000 to 4,000 mg daily, there was no correlation between somnolence and drug dosage.

Characteristics of the included studies of levetiracetam.

LEV study	Design	Inclusion criteria of patients	Groups (mg/d)	LEV No. (ITT)	Males, %	Age, y, (mean, SD)	Titration, w	Treatment duration, w	Duration of epilepsy, y	BSF, n/w median
Ben-Menachem [1]	RDBPCT	Having at least 2 partial seizures per month during baseline despite treatment with 1 AED	Placebo	105	49	37 (12)	4	16	19 (12)	1.8
			3000	181	48	36 (12)			19 (11)	1.7
Cereghino [13]	RDBPCT	Having partial seizures occurring monthly during baseline despite treatment with at least 2 AEDs	Placebo	95	52.6	38 (11)	4	18	–	1.8
			1000	98	63.3	38 (11)			–	2.5
			3000	101	65.3	38 (11)			–	2.0
Shorvon [16]	RDBPCT	Having seizures that persisted for at least the previous 2 years despite treatment with 1 or 2 AEDs	Placebo	112	49	37 (12)	4	12	23.2 (11.0)	2.5
			1000	106	48	36 (10)			23.8 (12.3)	2.8
			2000	106	48	37 (12)			23.6 (13.3)	2.6
Peltola [15]	RDBPCT	Having recurrent partial seizures despite receiving 1–3 AEDs	Placebo	79	59.5	32.38 (12.60)	Without	12	6.43 (11.9)	–
			1000	79	65.8	33.97 (13.41)			13.11 (10.8)	–
Tsai [17]	RDBPCT	Having partial seizures that were treatment resistant with at least 2 classic AEDs	Placebo	47	53.2	31.7 (8.2)	2	12	18.7 (10.7)	1.6
			2000	47	36.2	32.8 (10.5)			18.6 (8.5)	2.0
Wu [18]	RDBPCT	Having treatment-resistant partial seizures on 1 or 2 AEDs	Placebo	100	54.0	32.8 (11.9)	4	16	17.3 (12.1)	1.8
			3000	102	50.0	32.7 (13.4)			16.5 (12.7)	1.8
Xiao [19]	RDBPCT	Having at least 4 seizures per month despite therapy with other AEDs	Placebo	28	42.9	32.8 (11.2)	4	16	14.1 (9.4)	–
			3000	28	42.9	32.5 (11.2)			16.1 (12.5)	–
Inoue [14]	RDBPCT	Experiencing partial seizures at least twice per month when taking 1 – 3 AEDs, with a history of partial seizures for >2 years	Placebo	70	50.0	34.9 (12.56)	4	12	16.3 (11.9)	3.0
			500	71	49.3	33.2 (10.64)			16.4 (10.9)	2.7
			1000	70	41.4	32.8 (10.90)			14.5 (8.9)	2.7
			2000	70	50.0	30.4 (10.06)			13.8 (9.6)	3.2
			3000	70	52.9	33.1 (11.72)			15.2 (10.3)	2.7

LEV, levetiracetam; ITT, intent-to-treat; SD, standard deviation; BSF, baseline seizure frequency; RDBPCT, randomized, double-blind, placebo-controlled trial; AEDs, antiepileptic drugs.

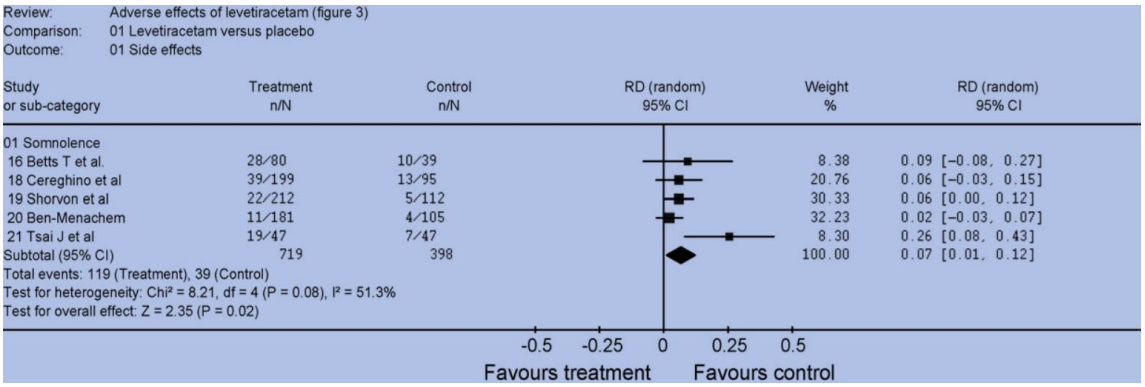


Figure 2: shows the risk difference (95% CI) of the CNS side effects that were significantly (P < 0.05) more common while using levetiracetam.

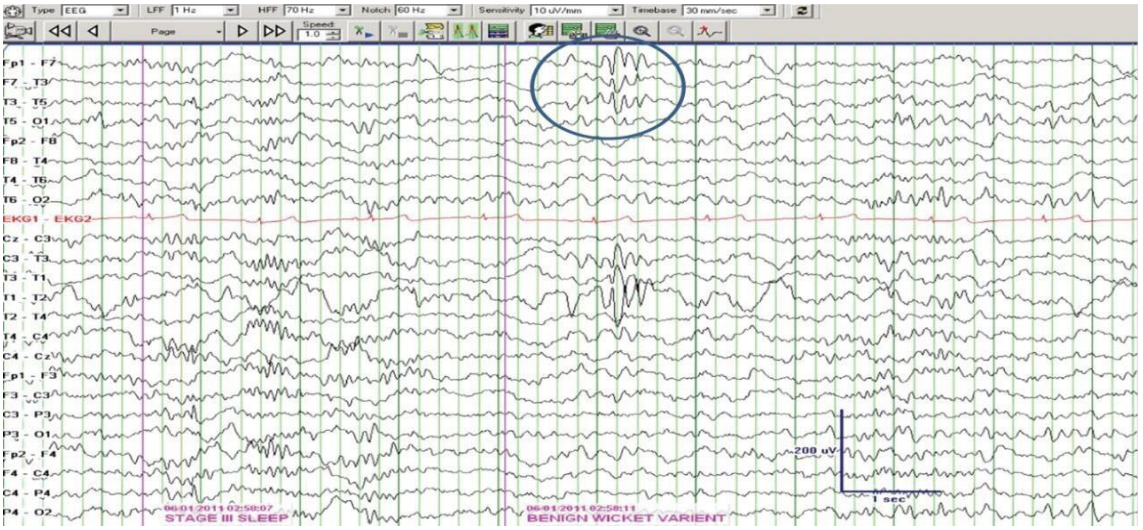
REFERAL DIAGNOSIS AND DIAGNOSIS FROM HISTORY

The referring physician made a specific diagnosis in 28.5% (45/158) of cases. The others,

which comprised patients who had experienced a "collapse," "blackout," or "loss of consciousness," lacked a precise diagnosis. Table 1 lists the referral sources, with primary care accounting for the majority of referrals. The overall diagnostic yield increased from 28% to 87% with the index neurology consultation. The statistical significance of this was very strong ($\chi^2 = 109.6$, $p < 0.0001$). With the exception of the subgroup of patients who had already seen a neurologist, where diagnostic concordance was 90%, there was generally little interobserver agreement in the diagnosis.

EEG

In this study, 7 out of 25 (28%) of the participants with epilepsy had an EEG yield. The identification of focal alterations (one) and generalized discharges (two) helped in the classification of three individuals who had previously received an epilepsy diagnosis. Focal slowing was observed in three epileptic patients. In two additional cases, focal slowing was noted. As shown in the diagram, epilepsy was identified.



CARDIAC INVESTIGATION

Carotid stimulation and tilt table testing were performed on three patients. In one case, the patient underwent permanent pacemaker placement after this validated a clinically suspected carotid hypersensitivity. Vasovagal syncope was confirmed in one patient, but another study found no abnormalities.

CASE REPORT

A right-handed retired builder, 60, arrived at the Epilepsy Clinic after experiencing multiple generalized tonic-clonic seizures over the course of eight months. Unexpected attacks were

followed by two to three hours of postictal disorientation and agitation. Some seizures arose directly from sleep and occurred in groups of three to five in the early morning. After receiving 600 mg of carbamazepine daily, his seizures stopped. He also believed that his amnesia had improved after starting antiepileptic medication therapy, which his family confirmed. However, he refused to undergo another neuropsychological evaluation.

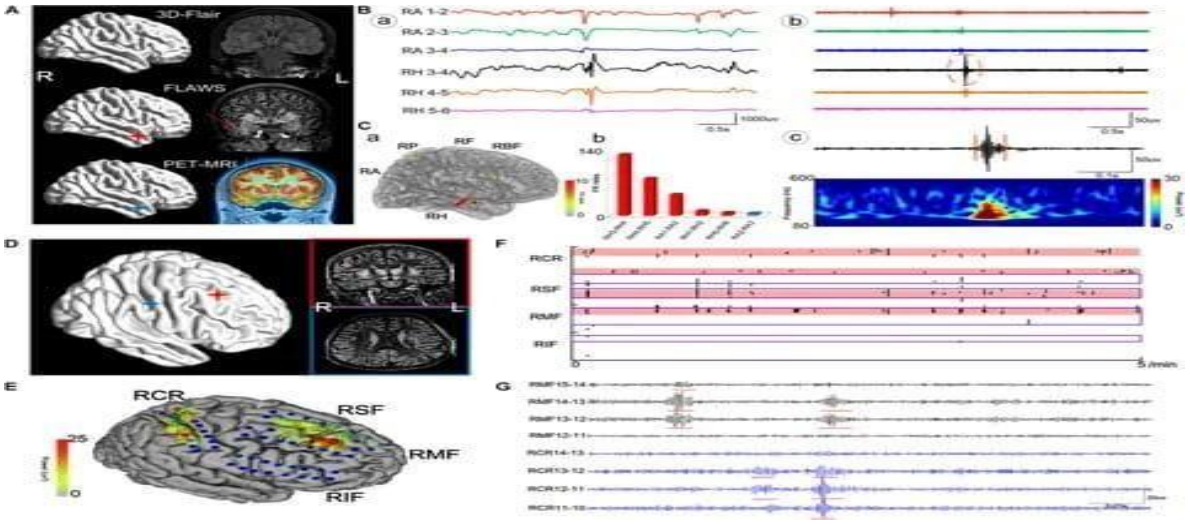
RISK FACTOR ANALYSIS

Phase two of the initial survey included the risk factor study, which required gathering data on a wide range of possible epilepsy risk factors. These were divided into sociodemographic factors and those that generally operate during the prenatal, perinatal, and postnatal phases of fetal and child development. Twelve variables were identified as possible risk factors for the onset of epilepsy following the initial univariate analysis. A history of symptoms suggestive of birth asphyxia, neonatal tetanus, jaundice, or sepsis was considered a neonatal insult for the purposes of this investigation.

CASE STUDIES

The MRI and 3D-FLAIR images of Patient #2 (Figures 4A–C), a 29-year-old man, showed no abnormalities despite his having tonic-clonic seizures for 24 years. PET and MRI fusion findings revealed right temporal lobe and right hippocampal hypometabolism, while FLAWS identified a lesion in the same region. Following automatic HFO detection, the right hippocampus and amygdala accounted for 72% of the channel distribution area of HFOs, consistent with the PET-MRI and FLAWS findings. After a year of follow-up, the patient was seizure-free following the removal of the right hippocampus, right temporal lobe, and right basis frontalis (small abnormal discharge). For 17 years, 20-year-old male Patient #11 (Figures 1D–F) suffered from tonic-clonic seizures or physical convulsions. The MRI results were normal. HFO analysis and FLAWS revealed abnormalities in the right frontal lobe and the regions around the posterior central sulcus. However, only the patient's right frontal lobe was removed, and the middle region was left untreated due to a lack of awareness regarding the significance of using FLAWS and HFOs, as well as the need to preserve the eloquent cortex. Consequently, following the procedure, the patient continued to experience seizures. Gray matter heterotopia in the left medial parietal lobe (near the ventricle) was suspected in Patient #1 (Figure 2), a 23-year-old man, and was evident on both PET-MRI and FLAWS scans. Channels in this region were not the EZ, according to the HFO analysis. This heterotopic region was not removed. One year after the procedure, the patient remained

seizure-free.



The cases of Patients #2 (A–C) and #11 (D–G) are shown in FIGURE 1. (A) Patient #2's neuroimaging findings. (B) Intracranial electroencephalogram (iEEG) signal (b) and raw data (a) following bandpass filtering (200–500 Hz) of several significant channels. (c) Our detector identified one FR. Right hippocampus (RH); right amygdala (RA). (C) HFO results displayed on Patient #2's brain model (a) and the ranking in descending order based on FR rates (b). The HFO threshold designates the suspect channels, which are highlighted in red. RBF stands for right basis of the frontal lobe; RF for right frontal lobe; and RP for right parietal lobe. (D) Patient #11's neuroimaging findings. (E) The brain model displays the FR rates. RIF stands for right inferior frontal lobe; RSF for right superior frontal lobe; RMF for right mesial frontal lobe; and RCR for right central areas. (F) The timing of each FR detected by our automatic detector in every channel over the course of a 5-minute iEEG segment. Each FR's timing and location are represented as points. The blue line indicates the resected area. The EZ is verified using our quantified threshold in the pink areas. HFOs identified one location that was undamaged. (G) The FRs that can be detected in various channels. The indicated anomalous locations are marked by the red arrows.

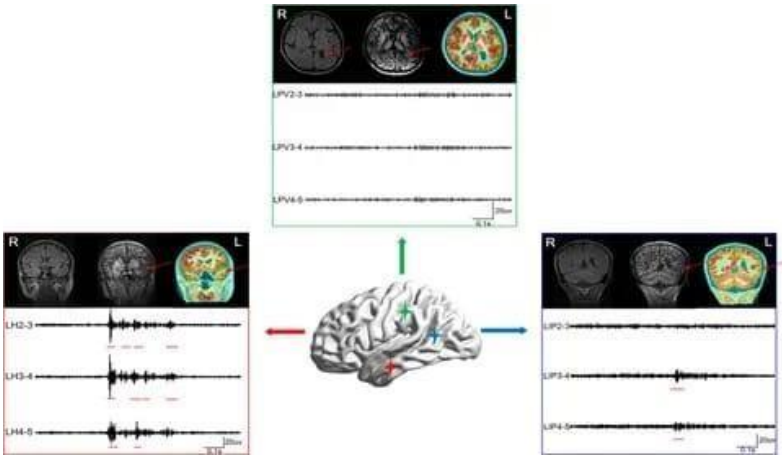


Figure 2: Patient #1's situation. Based on the MRI results, Patient #1 was suspected of having gray matter heterotopia in the left medial parietal lobe (around the ventricle), as the heterotopia was evident in both FLAWS and PET-MRI. Channels in this area showed significantly fewer FRs than those in the left hippocampus and left posterior temporal region, according to the HFO study. The three boxes highlight three lesions identified by FR findings(red lines) and neuroimaging (red arrows). LIP stands for left inferior frontal gyrus; LH for left hippocampus; and LPV for left periventricular area. The indicated anomalous locations are marked by the red arrows.

CONCLUSION

There aren't many medical facilities that specialize in epilepsy on social media. Most notably, most social media profiles do not adequately advocate for epilepsy surgery as a treatment for refractory seizures. To understand the biology of epilepsy and help develop new treatments and a cure for persistent epilepsies, it is necessary to improve the quality of epilepsy research conducted in India.

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